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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Dell'Orco et al.	
Appln. No.:	10/578,660	Group Art Unit: 1625
Filing Date:	May 9, 2006	Examiner: C. Aulakh
For:	NOVEL COMPOUND, CORRESPONDING COMPOSITIONS, PREPARATION AND/OR TREATMENT METHODS	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, Jeffery L. Wood, do solemnly declare that:

I received a BS degree in Chemistry from the Pennsylvania State University in 1980 and a PhD degree in Chemistry from the University of Rochester in 1986.

I have been employed by GlaxoSmithKline (formerly SmithKlineBeecham) since 1987 and have held a number of posts within the Synthetic Chemistry department. I currently hold the position of Team Manager, Synthetic Chemistry in the research facility located in King of Prussia, Pennsylvania.

Since receiving my PhD, I have worked for 22 years as a synthetic organic chemist, which includes analyzing and interpreting spectral data and in the past 9 years I have also worked closely in a matrix oversight capacity with spectroscopists characterizing the solid-state structure of chemical compounds using techniques including X-ray diffraction and infrared spectroscopy.

Topotecan is a compound having the chemical name: (S)-9-N,N-dimethylaminomethyl-10-hydroxycamptothecin. Topotecan monohydrochloride is a compound having the chemical name: (S)-9-N,N-dimethylaminomethyl-10-hydroxycamptothecin monohydrochloride salt.

For the purposes of this declaration, topotecan monohydrochloride salt is the solid (S)-9-N,N-dimethylaminomethyl-10-hydroxycamptothecin monohydrochloride salt prepared in accordance with the procedures of U.S. Patent No. 5,004,758. For the purposes of this declaration, topotecan monohydrochloride pentahydrate salt is the crystalline solid (S)-9-N,N-dimethylaminomethyl-10-hydroxycamptothecin monohydrochloride pentahydrate salt prepared in accordance with the procedures of U.S. Patent Application No. 10/578,660.

I. Topotecan monohydrochloride pentahydrate salt, (S)-9-N,N-dimethylaminomethyl-10-hydroxycamptothecin monohydrochloride salt, of U.S. Patent Application No. 10/578,660

[I-1] XRPD Analysis of the topotecan monohydrochloride pentahydrate of U.S. Patent Application No. 10/578,660

The X-ray powder diffraction pattern obtained for a sample of the topotecan monohydrochloride pentahydrate of U.S. Patent Application No. 10/578,660 is reproduced in Figure 1. The diffraction angles (° 2θ) and d-spacings (Angstroms) calculated from the acquisition data are reproduced in Table 1.

X-Ray Diffraction Acquisition Parameters

Scan range:	2 degrees two-theta to 35 degrees two-theta
Generator power:	40kV, 40mA
Radiation Source:	Cu K-alpha
Scan type:	Continuous
Step Time:	10.160 seconds
Sample Rotation:	25 rpm

Step Size:	0.0167 degrees two-theta per step
Incident Beam Optics:	fixed slits (0.5 degree aperture), 0.04 radian soller slits, 10mm beam mask
Diffracted Beam Optics:	Fixed slits (X'celerator module), 0.04 radian soller slits
Detector Type:	Philips X'Celerator RTMS (Real Time Multi Strip)

Table 1: X-Ray diffraction data for the topotecan monohydrochloride pentahydrate of U.S. Patent Application No. 10/578,660

Diffraction angle (° 2θ)*	D-spacing (Angstroms)
4.5	19.7
6.4	13.8
7.1	12.4
9.0	9.8
10.1	8.8
11.5	7.7
12.6	7.0
13.1	6.7
14.1	6.3
15.5	5.7
17.9	5.0
18.7	4.7
20.0	4.4
20.3	4.4
21.1	4.2
21.8	4.1
23.0	3.9
24.8	3.6
25.6	3.5
26.6	3.3
27.2	3.3
28.9	3.1

*Using copper K-alpha 1 radiation.

II. Topotecan monohydrochloride salt, (S)-9-N,N-dimethylaminomethyl-10-hydroxycamptothecin monohydrochloride salt, prepared in accordance with U.S. Patent No. 5,004,758

[II-1] Under my direction, topotecan monohydrochloride salt was prepared and analyzed as follows.

In Example 18 of US 5,004,758 , (S)-9-Dimethylaminomethyl-10-hydroxycamptothecin monohydrochloride salt was prepared from a solution of topotecan acetate salt (8.5 g, 14.5 mmol, which analyzed for 2.5 equivalents of acetic acid and 0.75 equivalents of water) in 0.1 N hydrochloric acid (170 mL, 17 mmol) by lyophilizing and pumping under vacuum for 3 days. For our experiments, this solution was reproduced by dissolving (S)-9-dimethylaminomethyl-10-hydroxycamptothecin free base (6.11 g, 14.5 mmol), glacial acetic acid (2.18 g, 36.2 mmol, 2.5 equivalents) and water (0.195 g, 10.9 mmol, 0.75 equivalents) in 170 mL of 0.1 N aqueous hydrochloric acid (17 mmol). A 50 mL portion of this solution was lyophilized and pumped under high vacuum for four days to give 2.2 g of (S)-9-dimethylaminomethyl-10-hydroxycamptothecin monohydrochloride salt. A second 50 mL portion of the solution was lyophilized and pumped under high vacuum for three days to give 2.1 g of (S)-9-dimethylaminomethyl-10-hydroxycamptothecin monohydrochloride salt.

[II-2] XRPD Analysis of topotecan monohydrochloride salt prepared in accordance with U.S. Patent No. 5,004758

The X-ray powder diffraction patterns obtained for the two samples of the topotecan monohydrochloride salt prepared as described in paragraph [II-1] are shown in Figure 2 (topotecan HCl sample lyophilized for 3 days) and Figure 3 (topotecan HCl sample lyophilized for 4 days). The acquisition parameters are provided below. Diffraction angles (° 2θ) and d-spacings (Angstroms) could not be calculated from the acquisition data because there are no distinguishable peaks in either of these diffraction patterns.

X-Ray Diffraction Acquisition Parameters

Scan range:	2 degrees two-theta to 40 degrees two-theta
Generator power:	40kV, 40mA
Radiation Source:	Cu K-alpha
Scan type:	Continuous
Step Time:	10.160 seconds
Sample Rotation:	60 rpm
Step Size:	0.017 degrees two-theta per step
Incident Beam Optics:	0.04 radian soller slits, 6mm programmable divergence slit, 10mm beam mask, and 0.5 degree anti-scatter slit
Diffracted Beam Optics:	6mm programmable anti-scatter slit assembly (X'celerator module), 0.04 radian soller slits
Detector Type:	Philips X'Celerator RTMS (Real Time Multi Strip)

III. Comparison of the XRPD data of the topotecan monohydrochloride pentahydrate salt of U.S. Patent Application No. 10/578,660 with the XRPD data of the topotecan monohydrochloride salt prepared according to the process of U.S. Patent No. 5,004,758

[III-1] I have compared the XRPD patterns (Figures 2 and 3) from the topotecan monohydrochloride salt samples described above with the XRPD pattern (Figure 1) from topotecan monohydrochloride pentahydrate salt of U.S. Patent Application No. 10/578,660 and it is very clear that they are different. In consultation with an X-ray spectroscopist, it was determined that the XRPD patterns of both samples of topotecan monohydrochloride indicate that these materials are nearly completely amorphous – the XRPD patterns provide no distinguishable form information. In contrast, the XRPD pattern provided by the topotecan monohydrochloride pentahydrate salt of U.S. Patent Application No. 10/578,660 is a clear pattern with sharp peaks (identified in Table 1), indicating that this material is crystalline.

IV. Conclusion

[IV-1] Accordingly, I believe that the crystalline form of the topotecan monohydrochloride pentahydrate salt of U.S. Patent Application No. 10/578,660 and the solid form of the topotecan monohydrochloride salt of U.S. Patent No. 5,004,758 are different. That is, the crystalline form of the topotecan monohydrochloride pentahydrate salt that provided the

XRPD pattern of Figure 1 is different from the amorphous form of the topotecan monohydrochloride salt that provided the XRPD patterns of Figure 2.

I declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that the willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: _____, this 19th day of May 2008.

Figure 1: XRPD pattern of topotecan monohydrochloride pentahydrate salt of U.S. Patent Application No. 10/578,660

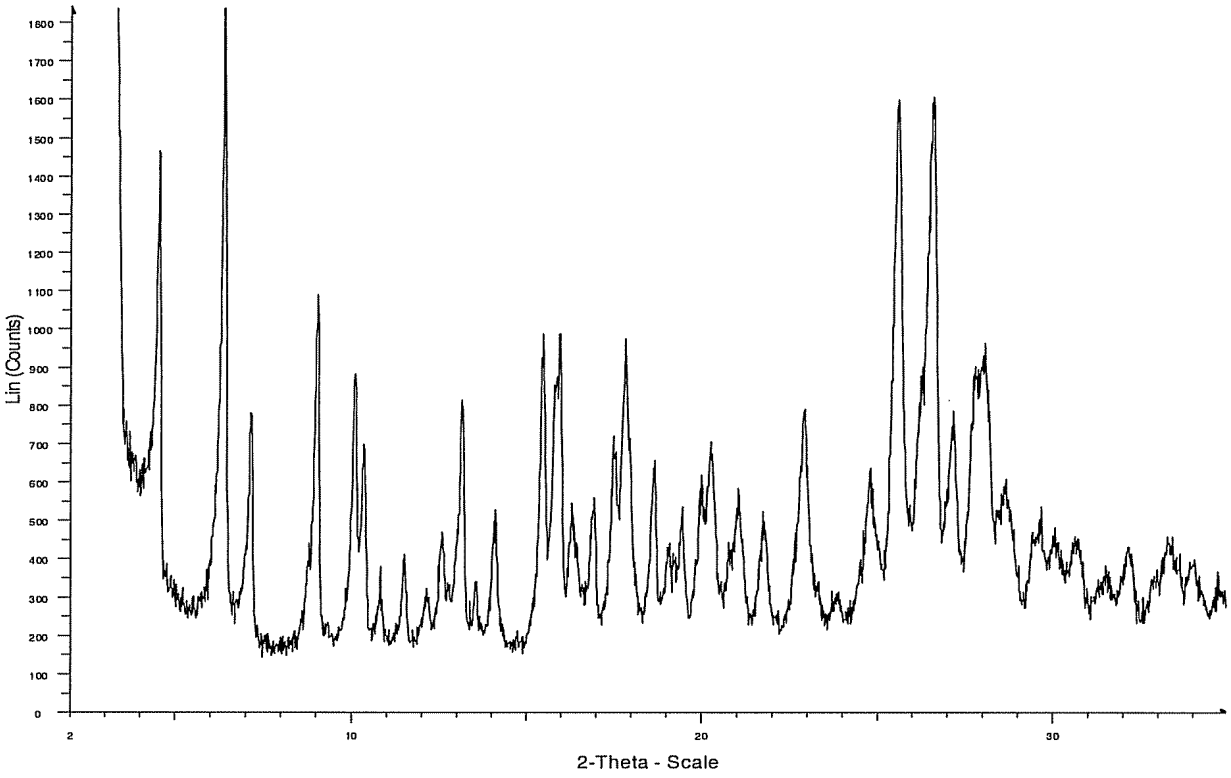

Figure 2: XRPD pattern of topotecan monohydrochloride prepared in accordance with the method of Example 18 of U.S. Patent No. 5,004,758 – 3 Days Lyophilization

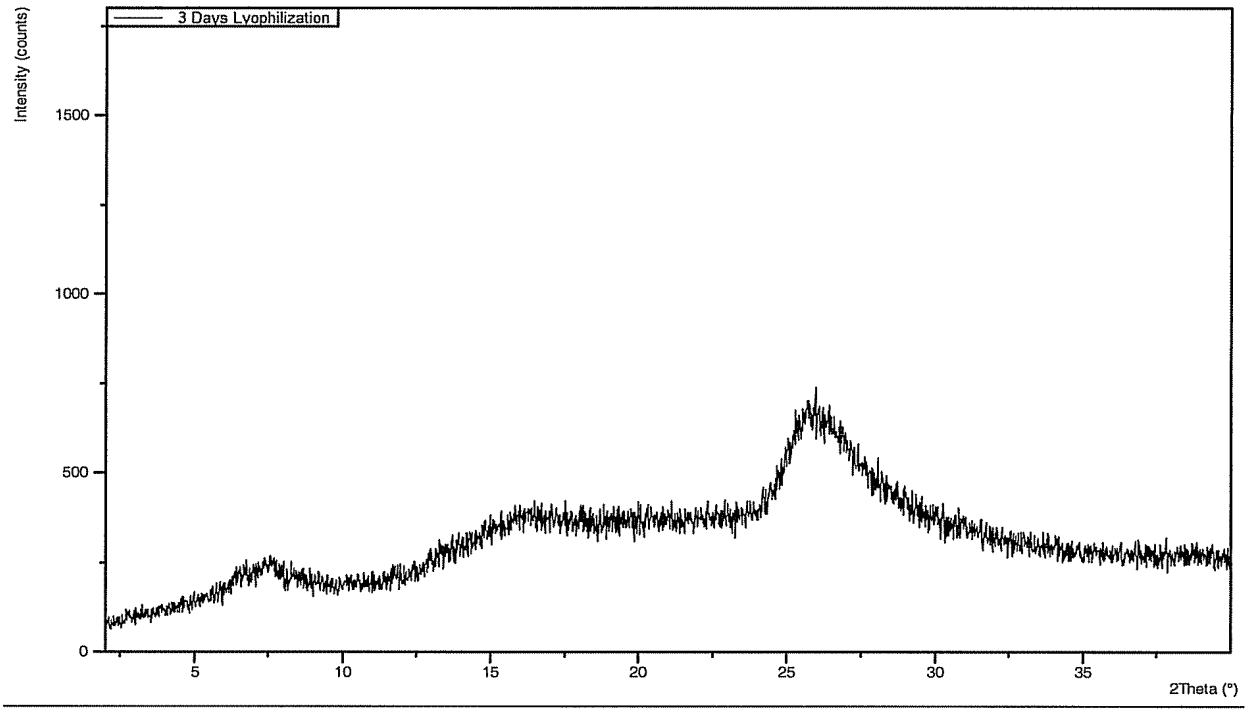

Figure 2: XRPD pattern of topotecan hydrochloride prepared in accordance with the method of Example 18 of U.S. Patent No. 5,004,758 – 4 Days Lyophilization